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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K		A2	(11) International Publication Number: WO 94/08551
			(43) International Publication Date: 28 April 1994 (28.04.94)
(21) International Application Number: PCT/US93/08887		(74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).	
(22) International Filing Date: 22 September 1993 (22.09.93)			
(30) Priority data: 07/955,013 9 October 1992 (09.10.92) US		(81) Designated States: AU, CA, FI, JP, KR, NO, NZ, RU, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
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(54) Title: PHARMACEUTICAL COMPOSITIONS AND METHODS FOR TREATING COLD SYMPTOMS			
(57) Abstract			
<p>Pharmaceutical compositions comprising a safe and effective amount of at least one pharmaceutical cold active; 3-1-menthoxy propane 1,2-diol; and a pharmaceutically-acceptable carrier material suitable for oral or nasal administration. The present invention also includes methods for treating cough, cold, cold-like, allergy and/or flu symptoms in a human or lower animal, said method comprising administering to a human or lower animal in need of such treatment, by oral or nasal administration, a composition comprising 3-1-menthoxy propane 1,2-diol.</p>			

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PHARMACEUTICAL COMPOSITIONS AND METHODS
FOR TREATING COLD SYMPTOMS

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BACKGROUND OF THE INVENTION

The present invention relates to orally or nasally administrable pharmaceutical compositions comprising at least one pharmaceutical active, 3-1-menthoxy propane 1,2-diol (herein referred to as "MPD") and pharmaceutically-acceptable carrier material(s). The present invention also relates to methods for treating cough, cold, cold-like, allergy and/or flu symptoms in a human or lower animal by administering, orally or nasally, a composition comprising MPD.

Pharmaceutical compositions safe and effective for treating colds, flu, and allergies are well known. Over-the-counter medications provide symptomatic relief of such illnesses. Typical symptoms of the common cold are mild malaise, sore throat and nasal complaints. Nasal discharge, nasal congestion and/or sneezing frequently are present. Also common are sore, dry or scratchy throat and hoarseness and cough. Other symptoms may include mild burning of the eyes, loss of smell and taste, a feeling of pressure or fullness in the sinuses or ears, headache, and vocal impairment. Flu symptoms are similar but usually of greater severity, including fever, generalized aches and pains, fatigue and weakness, and chest discomfort. Allergy symptoms are more akin to the common cold, with more frequent/severe sinus pressure, drainage and headaches.

— Prior art formulations for treating cough, cold, cold-like, allergy and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith typically contain one or more of the pharmaceutical actives which are analgesics, anesthetics, antihistamines, decongestants, cough suppressants, antitussives and expectorants.

It is an object of the present invention to provide compositions and methods useful for treating cough, cold, cold-like, allergy and flu symptoms in humans and lower animals in need of such treatment. Another object is to provide such compositions and methods having increased perceived efficacy, e.g., speed of relief and/or duration of relief, and/or improved aesthetics.

These and other objects of the present invention will become

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readily apparent from the detailed description which follows.

All percentages and ratios used herein are by weight, and all measurements are made at 25°C, unless otherwise specified.

SUMMARY OF THE INVENTION

5 The present invention is directed to pharmaceutical compositions comprising: (a) a safe and effective amount of at least one pharmaceutical cold active; (b) 3-l-menthoxy propane 1,2-diol; and (c) a pharmaceutically-acceptable carrier material suitable for oral or nasal administration.

10 The present invention is also directed to methods for treating cough, cold, cold-like, allergy, and flu symptoms in a human or lower animal, said method comprising administering to a human or lower animal in need of such treatment, by oral or nasal administration, a composition comprising 3-l-menthoxy propane 1,2-diol.

DETAILED DESCRIPTION OF THE INVENTION

15 The present invention relates to pharmaceutical compositions comprising: (a) at least one pharmaceutical cold active; (b) 3-l-menthoxy propane 1,2-diol ("MPD"); and (c) pharmaceutically-acceptable carrier material suitable for oral or nasal administration. The
20 components of the compositions according to the present invention, and representative amounts, as well as the present invention methods are described in detail as follows.

Pharmaceutical Cold Actives:

25 The pharmaceutical compositions according to the present invention comprise pharmaceutical cold actives useful for treating cough, cold, cold-like, allergy and/or flu symptoms. Such pharmaceutical actives are well known, and are generally recognized as being an active having analgesic, anti-inflammatory, anesthetic, antihistamine, decongestant, cough suppressant, demulcents, antitussive, and/or
30 expectorant properties.

35 The compositions of this invention therefore contain one or more known pharmaceutical cold actives, particularly those commonly utilized in cough/cold preparations, such as, for example, a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine and ephedrine, their pharmaceutically acceptable salts; an antitussive such as dextromethorphan, chlorphedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, menthol, hydrocodone, hydromorphone, fominoben, their pharmaceutically-acceptable salts; an expect-

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torant or mucolytic such as glyceryl guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine and bromhexine, ambroxol, their pharmaceutically acceptable salts; and an antihistamine such as chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbrompheniramine, triprolidine, azatadine, doxylamine, tripeleminamine, cyproheptadine, hydroxyzine, clemastine, carbinoxamine, phenindamine, bromodiphenhydramine, pyrilamine, their pharmaceutically acceptable salts, as well as the non-sedating antihistamines which include acrivastine, AHR-11325, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, and terfenadine, their pharmaceutically acceptable salts: all of these components, as well as their acceptable dosage ranges are described in the following: U.S. Patent 4,783,465 to Sunshine et al., issued November 8, 1988, U.S. Patent 4,619,934 to Sunshine et al., issued October 28, 1986, which are incorporated by reference herein. Also useful are bronchodilators such as terbutaline, atropine, aminophylline, epinephrine, isoprenaline, metaproterenol, bitoterol, theophylline and albuterol. Also used are analgesic compounds such as aspirin, acetaminophen, ibuprofen, and naproxen; and topical anesthetics/analgesics such as phenol, benzocaine, hexyl resorcinol, and dyclonine.

The compositions of the present invention comprise a safe and effective amount of at least one pharmaceutical cold active. The phrase "safe and effective amount", as used herein, means an amount of a compound or composition high enough when administered orally or nasally to significantly positively modify the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of the pharmaceutical cold active will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the specific pharmaceutical cold active employed, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician. Typically, the pharmaceutical cold active(s) comprise from about 0.001% to about 99.9%, by weight, of the pharmaceutical compositions of the present invention, preferably from about 0.001% to about 75%, and most prefer-

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ably from about 0.01% to about 30%.

3-1-Menthoxy Propane 1,2-Diol:

5 The pharmaceutical compositions of the present invention also comprise 3-1-menthoxy propane 1,2-diol ("MPD"). This material is described in detail in U.S. Patent 4,459,425, issued July 10, 1984 to Amano et. al, incorporated herein by reference in its entirety. While not to be limited by theory, it is believed that the benefits obtained by the use of MPD in the compositions of the present invention are the result of the unique cooling profile for this compound. MPD is 10 commercially available, being sold by Takasago Perfumery Co., Ltd., Tokyo, Japan.

MPD typically comprises from about 0.001% to about 10% by weight of the pharmaceutical compositions of the present invention, preferably from about 0.01% to about 5%, and most preferably from about 15 0.01% to about 0.5%.

Pharmaceutically-Acceptable Carrier Material:

The term "pharmaceutically-acceptable carrier materials", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for oral 20 and/or nasal administration to a human or lower animal. The term "compatible", as used herein, means that the components of the compositions of the present invention are capable of being commingled with the pharmaceutical cold active, and with each other, in a manner such that there is no interaction which would substantially reduce the 25 pharmaceutical efficacy of the compositions under ordinary use situations. Pharmaceutically-acceptable carrier materials must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human being treated.

The choice of pharmaceutically-acceptable carrier materials to be 30 used in conjunction with the pharmaceutical cold active of the present compositions is basically determined by the dose form for the compositions. The preferred dosage forms are liquid solutions, liquid suspensions, tablets, capsules and the like, comprising a safe and effective amount of the pharmaceutical actives. Pharmaceutically- 35 acceptable carrier materials suitable for the preparation of dosage forms for oral and nasal (e.g., nasal sprays) administration are well-known in the art. Their selection will depend on secondary considerations like taste, cost, shelf stability, which are not

critical for the purposes of the present invention, and can be made without difficulty by a person skilled in the art. Preferably the present invention compositions comprise from about 0.1% to about 99.99% of one or more pharmaceutically-acceptable carrier materials.

5 Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules, lozenges and bulk powders and liquid forms such as syrups and suspensions. These oral forms comprise a safe and effective amount of the pharmaceutical cold active component. Solid oral dosage forms preferably contain from about 0.1% to about
10 99%, more preferably from about 25% to about 99%, and most preferably from about 50% to about 99% of the pharmaceutical cold active component. Liquid oral dosage forms preferably contain from about 0.001% to about 25% and more preferably from about 0.001% to about 10% and most preferably from about 0.01% to about 5% of the pharmaceutical
15 cold active component.

Tablets can be compressed, molded, triturated, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, preservatives and flow-inducing agents. Also useful
20 are soft gelatin capsules.

Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms," Modern Pharmaceutics, Vol. 7, (Banker and Rhodes, editors), 359-427 (1979), incorporated by reference herein. Techniques and compositions for making
25 tablets (compressed and molded), capsules (hard and soft gelatin) and pills are described in Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (1980), incorporated herein by reference.

Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, pseudo emulsions, suspensions, and solutions and/or
30 suspensions reconstituted from non-effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, coloring agents, and flavoring agents. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms; are described
35 in U.S. Patent 3,903,297, Robert, issued September 2, 1975, incorporated by reference herein. Although water itself may make up the entire carrier, typical liquid formulations preferably contain a co-solvent, for example, propylene glycol, polyethylene glycol,

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alcohol, glycerin, sorbitol solution and the like, to assist solubilization and incorporation of water-insoluble ingredients, such as flavoring oils and the like into the composition.

Other optional ingredients well known to the pharmacist's art may also be included in amounts generally known for these ingredients, for example, natural or artificial sweeteners, flavoring agents, colorants and the like to provide a palatable and pleasant looking final product, antioxidants, for example, butylated hydroxy anisole or butylated hydroxy toluene, and preservatives, for example, methyl or propyl paraben, potassium sorbate, or sodium benzoate, to prolong and enhance shelf life. A preferred optional component is also materials other than MPD having cooling properties, such as menthol and menthol-like compounds such as N-ethyl-p-menthane-3-carboxamide (preferably at from about 0.001% to about 5%, more preferably from about 0.001% to about 0.5%), and mixtures thereof. A preferred optional component is also caffeine.

Method of Treatment:

The present invention also relates to a method for treating cough, cold, cold-like, allergy and flu symptoms in a human or lower animal. Said method comprises administering to a human or lower animal in need of such treatment, by oral or nasal administration, a composition comprising MPD. Preferred pharmaceutical compositions for administration according to the present invention method comprise from about 0.001% to about 10% (preferably from about 0.01% to about 0.5%) of MPD, and from about 0.1% to about 99.999% (preferably from about 70% to about 99.99%) of pharmaceutically-acceptable carrier material(s). Preferred is administering, either orally or nasally, a safe and effective amount of a composition according to the present invention. Most preferred is oral administration.

The following examples further describe and demonstrate embodiments within the scope of the present invention. These examples are given solely for the purpose of illustration and are not to be construed as a limitation of the present invention as many variations thereof are possible without departing from the spirit and scope.

Example 1 - Cough Syrup

<u>Ingredient</u>	<u>Amount/15ml dose</u>
Dextromethorphan HBr	20 mg
Glyceryl Guaiacolate	200 mg

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	Sucrose	8.16 grams
	Alcohol	1 ml
	Citric Acid, Anhydrous	4 mg
	Sodium Citrate	300 mg
5	MPD1)	15 mg
	WS-32)	0.75 mg
	Menthol	7.5 mg
	Coloring Agent	4.5 mg
	Water, Purified	Q.S. to 15 ml
10	1) 3-1-menthoxy propane 1, 2-diol, supplied by Takasago Perfumery Co., Ltd., Tokyo, Japan	
	2) N-ethyl-p-menthane-3-carboxamide, supplied by Sterling Drugs	

This composition is prepared by first dissolving the dextromethorphan and glyceryl guaiacolate in alcohol and then adding with constant mixing the menthol, MPD and WS-3. In separate containers dissolve the sucrose in a small portion of the water, dissolve the coloring agent in a separate small portion of the water, and in still another container dissolve the sodium citrate and citric acid in a small portion of the water. Finally, all the premixes and the remaining water are mixed with constant mixing to prepare a composition of the present invention having 20 mg of dextromethorphan and 200 mg of glyceryl guaiacolate per 15 ml of composition.

Administration (by drinking 15 ml) of this composition to a human patient having a cough associated with the common cold provides rapid, long-lasting relief of the cough in said human patient.

Example 2 - Cough Drop

		% Composition
		(% W/W)
30	Menthol, Natural	0.2211
	Eucalyptus Oil	0.1455
	MPD	0.0700
	WS-3	0.0300
	FD&C Blue #1	0.0022
35	Sugar	QS*
	Low DE Corn Syrup	QS*
	*60/40 Sugar/Low DE Corn Syrup (before cook); candy base used.	

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This composition is prepared by standard drop forming techniques.

Administration (by sucking) of drops to a human patient having a cough associated with the common cold provides rapid, long lasting relief of the cough in said human patient.

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WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:
 - (a) a safe and effective amount of at least one pharmaceutical cold active;
 - (b) 3-1-menthoxy propane-1,2-diol; and
 - (c) pharmaceutically-acceptable carrier material suitable for oral or nasal administration.
2. A pharmaceutical composition comprising:
 - (a) from 0.001% to 99.9% of at least one pharmaceutical cold active;
 - (b) from 0.001% to 10% of 3-1-menthoxy propane 1,2-diol; and
 - (c) from 0.1% to 99.99% of pharmaceutically-acceptable carrier material suitable for oral or nasal administration.
3. A pharmaceutical composition comprising:
 - (a) from 0.01% to 30% of at least one pharmaceutical cold active;
 - (b) from 0.01% to 0.5% 3-1-menthoxy propane 1,2-diol; and
 - (c) from 70% to 99.99% of pharmaceutically acceptable carrier material suitable for oral or nasal administration.
4. The pharmaceutical composition according to any of Claims 1-3 wherein the pharmaceutical cold active is selected from the group consisting of analgesics, anti-inflammatories, anesthetics, antihistamines, decongestants, cough suppressants, demulcents, antitussives, expectorants, and mixtures thereof.
5. The pharmaceutical composition according to any of Claim 1-4 wherein the pharmaceutical cold active is selected from the group consisting of pseudoephedrine, phenylpropanolamine, phenylephrine, ephedrine, dextromethorphan, chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, menthol, hydrocodone, hydromorphone, fominoben, glyceryl guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine and brom-

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hexine, ambroxol, chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbrompheniramine, triprolidine, azatadine, doxylamine, tripeleminamine, cyproheptadine, hydroxyzine, clemastine, carbinoxamine, phenindamine, bromodiphenhydramine, pyrillamine, acrivastine, AHR-11325, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, terfenadine, terbutaline, atropine, aminophylline, epinephrine, isoprenaline, metaproterenol, bitoterol, theophylline, albuterol, aspirin, acetaminophen, ibuprofen, naproxen, phenol, benzocaine, hexyl resorcinol, dyclonine, the pharmaceutically acceptable salts thereof, and mixtures thereof.

6. The pharmaceutical composition according to any of Claims 1-5 further comprising a material in addition to 3-1-menthoxy propane 1,2-diol having cooling properties.
7. The pharmaceutical composition according to Claim 6 wherein the additional material having cooling properties is selected from menthol, N-ethyl-p-menthane-3-carboxamide, and mixtures thereof.
8. The pharmaceutical composition according to any of Claims 1-7 further comprising from 0.001% to 5% of N-ethyl-p-menthane-3-carboxamide.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 47/10, 9/00		A3	(11) International Publication Number: WO 94/08551 (43) International Publication Date: 28 April 1994 (28.04.94)
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(71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventors: UPSON, James, Grigg ; 11268 Springfield Pike, Springdale, OH 45246 (US). RUSSELL, Carmelita, Macklin ; 607 Vincennes Court, Cincinnati, OH 45231 (US).		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 23 June 1994 (23.06.94)	
(54) Title: PHARMACEUTICAL COMPOSITIONS AND METHODS FOR TREATING COLD SYMPTOMS			
(57) Abstract Pharmaceutical compositions comprising a safe and effective amount of at least one pharmaceutical cold active; 3-1-menthoxy propane 1,2-diol; and a pharmaceutically-acceptable carrier material suitable for oral or nasal administration. The present invention also includes methods for treating cough, cold, cold-like, allergy and/or flu symptoms in a human or lower animal, said method comprising administering to a human or lower animal in need of such treatment, by oral or nasal administration, a composition comprising 3-1-menthoxy propane 1,2-diol.			

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 93/08887

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K47/10 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO, A, 92 17164 (THE PROCTER & GAMBLE COMPANY) 15 October 1992	1-8
Y	see claims 1, 3, 5, 10, 11 see page 5, line 16 - line 24 see page 6, line 1 - line 11	1-8
Y	FR, A, 2 127 011 (WILKINSON SWORD LIMITED) 13 October 1972 see claim 1 see page 10, line 5 - line 22	1-8

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☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

29 April 1994

Date of mailing of the international search report

18.05.94

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 93/08887

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